REMARKS

Claims 1-25 are currently pending in this application. Claims 1, 2 and 10-19 are currently withdrawn. Claims 3-6 and 20-25 have been amended to recite "enantiomerically pure L-methadone or a mixture of DL methadone having at least 65% L-methadone". Support for this amendment can be found throughout the specification as originally filed, for example, at Page 11, lines 7-15. No new matter has been added by these amendments. Accordingly, claims 1-25 will remain pending in the application.

Table 1 has been replaced to include the cut off portion of the original publication. This table was submitted in the original PCT filing. (A copy of the originally filed page is submitted herewith as Exhibit A). No new matter has been added.

Amendment of the claims should not be construed as acquiescense to any of the rejections set forth in the Office Action and was done solely to expedite prosecution of the application. Applicant respectfully reserves the right to pursue the claims as orginally filed or similar claims as well as any non-elected, canceled or otherwise unclaimed subject matter in one or more continuation, continuation-in-part, or divisional applications.

Reconsideration and withdrawal of the objections to this application in view of the amendments and remarks herewith, are respectfully requested, as the application is in condition for allowance.

Priority Claim

The Examiner has denied the instant application the benefit of the filing date of PCT International Application PCT/US03/09766 (March 27, 2003) or of Provisional application Ser. Nos. 60/367,790 (March 27, 2002) and 60/416,414 (October 7, 2002) due to the spelling of the inventor's last name on the executed declaration. This spelling is a typographical error made without deceptive intent on the part of the Applicant. The name "Gavril W. Pasternark" should be correctly spelled **Gavril W. Pasternak**. An application data sheet with the correct spelling is provided herewith.

According to M.P.E.P. §201.03 Examiner's note "A request under 37 CFR 1.48 will not be required: (B) Where a typographical or transliteration error in the spelling of an inventor's name is discovered, the Office should simply be notified of the error. A new oath or declaration is not required.... Reference to the notification will be made on the previously filed oath or declaration."

A Notification of Typographical Error in Executed Declaration is submitted herewith. As such, Applicant respectfully requests reference of this correction be made on the original declaration filed. Furthermore, Applicant respectfully request reconsideration amd acknowledgemetn of the priority claims made in the instant application as orginally filed. Accordingly, Applicant submits that the earliest effective filing date of the application is March 2, 2002, the filing date of Provisional application Ser. No. 60/367,790.

Rejections under 35 U.S.C. §102 (b)

Claims 3-5, 7-9 and 20-25 are rejected under 35 U.S.C. §102 (b) as being anticipated by Bolan et al.. *J. Pharm. Exp. Ther.* 303:557-562, 2002 ("Bolan"). Applicant respectfully points out that upon reconsideration of the priority claim in the instant application, the Bolan reference will no longer be applicable as §102(b) (publication date after March 27, 2002). As such, Applicant respectfully requests this rejection be withdrawn

Claims 3-4, 7-9 and 22-25 are rejected under 35 U.S.C. §102 (b) as being allegedly anticipated by Smith et al.. *Journal of Pharmacology and Experimental Therapeutics*. 108: 336-339 (1954) ("Smith"). The Examiner alleges that Smith teaches a method of providing analgesia to rats by administering a racemic methadone (and thereby L-methadone) and morphine by subcutaneous injection.[1]

As described above, Claims 3 and 4 have been amended to recite that the pharmaceutical composition comprises "enantiomerically pure L-methadone or a mixture of DL methadone having at least 65% L-methadone."

[1] The Examiner further alleges that the ability of compositions comprising L-methadone and morphine to potentiate an antinociceptive response is inherently present. Applicants respectfully disagree with this statement even though no further statement is made in light of the arguments presented above.

The Examiner states that "the methadone taught by Smith is considered to be a racemic mixture of D and L [stereoisomers]." As such, Smith does not teach the administration of enantiomerically pure L-methadone or a mixture of D- and L- methadone having at least 65% L-methadone. As Smith does not disclose all of the elements of the instant claims, it cannot anticipate the claims instant invention presented herein. Applicant respectfully requests reconsideration and withdrawal of the rejection.

Rejections under 35 U.S.C. §103 (a)

Claim 6 is rejected under 35 U.S.C. §103(a) as being obvious over Bolan. As discussed above, upon reconsideration of the priority claim in the instant application, the Bolan reference will no longer be applicable as §102(b) and therefore will also be unavailable under §103(a). As such, Applicant respectfully requests this rejection be withdrawn

Claims 5-6 and 21-22 are rejected under 35 U.S.C. §103(a) as being obvious over Smith in view of United States Patent No. 6,008,258 to Inturrisi ("Inturrisi").

To properly determine a *prima facie* case of obviousness, the Examiner "must step backward in time and into the shoes worn by the hypothetical 'person of ordinary skill in the art' when the invention was unknown and just before it was made." M.P.E.P § 2142. This is important as "impermissible hindsight must be avoided and the legal conclusion must be gleaned from the prior art." *Id.* Four factual inquiries must be made: first, a determination of the scope and contents of the prior art; second, a determination of the differences between the prior art and the claims in issue; third, a determination of level of ordinary skill in the pertinent art; and fourth, an evaluation of evidence of secondary consideration. *Graham v. John Deere,* 383 U.S. 1, 17-18, 148 USPQ 459, 467 (1966). Three criteria may be helpful in determining whether claimed subject mater is obvious under 103(a): first, if there is some suggestion or motivation to modify or combine the cited references; second, if there is a reasonable expectation of success; and third, if the prior art references teach or suggest all the claim limitations. *KSR Int'l Co. v. Teleflex, Inc.* No 04-1350 (U.S. Apr. 30, 2007). With regard to the first criterion, the mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.3d 690

(Fed. Cir. 1990). "Knowledge in the prior art of every element of a patent claim ... is not of itself sufficient to render claim obvious." *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966); *Teleflex*, [*Inc. v. Ficosa N. Am. Corp.*, 299 F.3d 1313, 1333-34 (Fed. Cir. 2002)]. The issue is whether there is an apparent reason to combine the known elements in the fashion claimed by the patent at issue. *KSR Int'l Co. v. Teleflex, Inc.*

As discussed above, Smith does not teach or suggest the administration of enantiomerically pure L-methadone or a mixture of D- and L- methadone having at least 65% L-methadone.

The Examiner relies on Inturrisi to rectify the deficiencies of Smith. In particular, the Examiner alleges that Inturrisi teaches that the L-isomer of methadone is responsible for the opioid properties of methadone and that L-methadone produces dose-dependent antinociception in rats. As such, the Examiner alleges that "it would have been obvious to one of ordinary skill in the art at the time of the invention to employ an increased amount of the active L-isomer of methadone."

Applicant respectfully submits that the Examiner has failed to estabilish a *prima facie* showing of obviousness because one of ordinary skill in the art would not have been motivated to combine the teachings of Smith and Inturrisi. In particular, Applicant contends that Inturrisi teaches away from combination with Smith as Inturrisi clearly seeks to avoid the tolerance and physical dependence, which are consequences of the chronic administration of morphine and morphine-like opioids.

Indeed, Inturrisi seeks to promote the use of nonopioid drugs that could attenuate and/or reverse opioid tolerance and physical dependence and that could be used in the opioid addict to assist in opioid detoxification. Because Inturrisi attributes the opioid properties of racemic methadone to the L-isomer, one of ordinary skill in the art, upon reading Inturrisi would not have had the necessary motivation to combine L-methadone with morphine without risk of creating a greater dependence.

As such, one of ordinary skill in the art, upon reading Inturrisi would not have been motivated to utilize enantiomerically pure L-methadone or the mixture of DL methadone having at least 65% L-methadone as Inturrisi teaches that this would likely provide opioid analgesia and

thus potentially negative effects of opioids described by Inturrisi. Moreover, one of ordinary skill in the art, upon reading Inturrisi would have been more likely to utilize enantiomerically pure D-methadone so as to avoid those side effects.

As Inturrisi teaches away from the desirability of combining the references, Applicants respectfully submit that rejection under 35 U.S.C. §103(a) should be withdrawn.

Although Applicants contend that the Examiner has not made out a *prima facie* case of obviousness of the claimed methods, Applicant respectfully submits that the compounds recited in the presently-pending claims have unexpected properties such that any possible *prima facie* case of obviousness is rebutted.

The Examiner states that it is the applicant's burden to demonstrate unexpected results over the prior art with regards to the synergy of the two active agents. In fact, Applicant has already provided evidence of unexpected results.

Thus, in Example 1 (Page 15), Applicant provides a table (reproduced herein) which shows the relative potency of L-methadone, D-methadone, morphine, M6G, codeine, 6-acetylmorphine and fentanyl using a radiant heat tail-flick assay. The combination of L-methadone with each drug resulted in a potency 3-4 times greater than the expected additive effect of the two drugs. Similarly, in Example 2 (Page 16), the same test was performed with morphine in combination with the other opioids instead of L-methadone. In each case, only additive effects were observed. Finally, in Example 3 (Page 17), Applicant showed that even at a dose 8 times higher than that of L-methadone, D-methadone did not have an influence on the morphine response whereas the L-methadone combination showed a 3-4 times greater effect.

Applicant respectfully submits that, absent the teachings of the present specification, one of ordinary skill in the art at the time this invention was made would not have had a reasonable expectation that compounds according to the present claims could be used according to the claimed methods.

As such, Applicant respectfully urges that the Smith and Inturrisi, whether taken alone or in combination, cannot and do not teach or suggest the invention of the claims under consideration; and thus, rejection under 35 U.S.C. §103(a) should be withdrawn.

CONCLUSION

In view of the amendments and remarks made herein, Applicant submits that the application is in condition for allowance. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are respectfully requested. If a telephone conference with Applicant's representative would be helpful in expediting prosecution of the application, Applicant invites the Examiner to contact the undersigned at the telephone number indicated below.

Applicant believes that no additional fees, other than the fee for the three-month extension of time, are required in connection with this paper. Nevertheless, Applicant authorizes the Director to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to Deposit Account No. 04-1105, under Order No. 62076(51590).

Date: November 13, 2008

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Exhibit A

The relative potencies of a series of μ-opioids were determined by their effective dosage (ED_{50}) values from dose-response curves. These values are given in Table 1.

Table 1: ED_{50} values of drugs alone and in combination with L-methadone

Drug	ED50 Value (mg/kg s.c.)			
	Drug alone	Combination (Total Drug Dose)		Potency Enhancement
		Observed	Additive (predicted)	
L-Methadone	1.9 ± 0.2			
D-Methadone	>> 4			
Morphine	4.7 ± 1.1	0.83 ± 0.12	3.11 ± 0.32	3.75 (P<0.002)
M6G	3.7 ± 0.4	1.03 ± 0.34	2.80 ± 0.21	2.73 (P<0.001)
Codeine	3.7 ± 0.4	0.74 ± 0.10	2.79 ± 0.22	3.78 (P<0.001)
6-Acetylmorphine	0.20 ± 0.03	0.27 ± 0.05	1.08 ± 0.09	3.94 (P<0.001)
Fentanyl	0.021 ± 0.005	0.79 ± 0.09	0.89 ± 0.09	1.13 (NS)

Male CD-1 mice (25-30 g in weight) were purchased from Charles River Laboratories, Inc (Wilmington, MA). All drugs used were obtained from the Research Technology Branch of the National Institute on Drug Abuse (Rockville, MD). Drugs were administered systemically via subcutaneous injections. Analgesia was assessed 30 minutes post-injection using radiant heat tail-flick assay. Baseline latencies ranged between 2.0 and 3.2 seconds. A maximal cutoff latency of 10 seconds was set to minimize tissue damage. Analgesia was assessed quantally as a doubling or greater of the baseline latency for each mouse. Quantal measurements are well known and are described in D'Amour, F.E. and Smith, D.L. (1941) *J. Pharmacol. Exp. Ther.* **72**: 174-179; and in Pasternak, G.W. et al. (1980a) *J. Pharmacol. Exp. Ther.* **214**: 455-462. Groups of mice were compared using Fisher's exact test. ED_{50} values and 95% confidence limits were calculated by probit analysis as described in Tallarida, R.J. (2000) *Drug Synergism and Dose Effect Data Analysis*. Chapman and Hall/CRC Press, Boca Raton, FL. The statistical